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AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph on page 1, lines 8-9 with the below amended paragraph.

This application is the National Stage application of International Application No. PCT/US99/16940 filed July 27, 1999 which ~~This application~~ claims benefit of priority to United States provisional patent application serial number 60/094,286, filed July 27, 1998, which is hereby incorporated by reference in its entirety.

Please replace the paragraph on page 18, lines 19-20 with the below amended paragraph.

Figure 8 depicts the effects of heating on mitochondrial uncoupling and correlation of uncoupling to superoxide free radical formation. Figure 8a shows the relationship between mitochondrial respiratory control ratio and superoxide production. Figure 8b shows the relationship between mitochondrial uncoupling and superooxide free radicals.

On page 90, line 21, please insert the following reference citations.

238.) de las Alas, V. et al (1990) " Oxygen Uptake and Mean Blood Pressure as Indicators of Induced Hyperthermia" J. Clinical Monitoring Volume 6(3):186-188.

239.) Scott, J. C. et al (1968) "Influence of 2,4 –Dinitrophenol on Myocardial Metabolism in Hemodynamics" Metabolism 17:370-376.

240.) Levine, S. et al (1975) "Ventilatory Response to Drug-Induced Hypermetabolism" J. Appl. Physio. Volume 38(5):827-833.

241.) Tainter, M. L. (1934) "Dintrophenol in Diet, on Growth and Duration of Life of the White Rat" Proc. Soc. Exper. Biol. Med., 31:1161-1162.

Please replace the paragraph on page 4, lines 15-29 with the below amended paragraph.

Body temperature is a critical factor in determining host susceptibility, location of lesions, and the natural history of many infectious diseases. Temperature has direct effects on the growth of all microorganisms, including those that are pathogenic. Almost all of the bacteria that cause disease in humans grow optimally within the range of 33-41^0 C and, their temperature growth characteristics are not easily altered in vitro. By example, the lesions of Hansen's disease (leprosy) caused by Mycobacterium leprae, characteristically grow and destroy the most acral, coolest parts of the body such as fingers, toes, external ear, the air-stream cooled nasal alae and larynx. Leprosy organisms proliferate and follow the coolest temperature gradients in the body, 25-33^0 C. In animals, the leprae organisms can only be grown in the armadillo or foot pads of mice ~~were~~ where the in situ lesion temperatures are 27-30^{0}C. Spontaneous improvement in leprosy lesions have been reported in patients following febrile illness. Fever therapy, hot baths and local heat therapy were formerly utilized in treating this disease. Hyperthermia is also known to destroy Treponema pallidum, the causative agent of syphilis, by heating five hours at 39^0 C, three hours at 40^0 C, two hours at 41^0 C or one hour at 41.5^0 C. The spirochetes responsible for yaws, bejel, pinta and Lyme disease show similar temperature sensitivity.

Please replace the paragraph on page 19, line 26 through page 2, line 2 with the below amended paragraph.

Pyruvic acid molecules derived from glucose, as well as end products of fat and protein breakdown, are transported into the mitochondrial matrix ~~were~~ where they are converted into 2 carbon fragments of acetylcoenzyme A, Figure 2. As depicted, these acetyl fragments enter the TCA cycle were their hydrogen atoms are removed and released as either hydrogen ions (H+) or combined with nicotinamide and flavin adenine dinucleotides (NAD+ and FADH) to produce large quantities of usable reducing equivalents (NADH and FADH2). The carbon skeleton is converted to carbon dioxide (CO2) which becomes dissolved in body fluids. Ultimately the dissolved CO2 is transported to the lungs and expired from the body. As noted in Figure 2, the flux of reactants in the TCA cycle is always in the same direction because NADH and FADH2 is constantly removed as hydrogen is oxidized by the mitochondrial electron transport chain.

Please replace the paragraph on page 25, lines 5-31 with the below amended paragraph.

Glycolysis and its associated heat production in the cytoplasm is also increased by DNP. Glycolytic activity is increased by reduced concentration ratios of ATP to ADP, activating ~~puruvate~~ pyruvate dehydrogenase and phosphofructokinase respectively (see Figure 1). These enzymes increase the rate of glucose catabolism to pyruvate and its conversion to acetyl-CoA for entry into the TCA cycle. Glycolysis is very "energy inefficient" in making up the energy equilibrium shortfall created by DNP. Uncaptured energy from the glycolytic exergonic reactions accelerated by DNP is released as heat in the cytoplasm. DNP stimulated anaerobic heat production through glycolysis can oftentimes be greater than that produced by the mitochondria. By example, many tumors and normal fibroblasts treated with DNP increase heat production by 83%, with only a 36% increase in oxygen consumption. Glycolysis is known to contribute greater than 62% of the total heat produced by human lymphocytes. Circled effect 14 shows that the mitochondrial electron transport chain normally produces reactive oxygen species through the univalent reduction of oxygen [see Figure 7, 7(a) & 7(b)]. Under physiologic conditions, 2 to 4% of mitochondrial oxygen is converted to superoxide. DNP induced partial uncoupling and mitochondrial heating increases reactive oxygen species production manifold. Cytochrome oxidase and reductase is known to be inhibited by heating of the electron transport system. As a result, heated mitochondrial membranes produce increased amount of oxygen free radicals when DNP induced uncoupling is stopped and oxygen consumption is normalized (see Figure 9). Reactive oxygen species act in synergy with heat to alter proteins, induce membrane changes and initiate apoptosis in susceptible cells. Circled effects 15 and 16 shows the effects of DNP on intracellular calcium homeostasis. Normally calcium is stored in the mitochondrial matrix, being pumped by the energized mitochondrial membrane. By DNP directly de-energizing mitochondria, and indirectly inducing membrane heating and prooxidant stress, inner mitochondrial membrane permeability is non-specifically increased with calcium efflux and cycling. This activates intramitochondrial dehydrogenses to produce more reducing equivalents in the form of NADH and FADH2 to match increased energy demands. Heat production is increased as a byproduct from the augmented TCA cycle.

Please replace the paragraph on page 12, line 25 through page 13, line 8 with the below amended paragraph.

By necessity, therefore, prior art heating methods require high external temperatures to establish a sufficient gradient to overcome the nonisotropic and non-homogeneous conductive heat loss between internal tissues and the insulating barrier of the cellular and mitochondrial membranes. For example, the Organetics PSI® (perfusion system) (now First Circle Medical Inc.) device has to heat blood externally to 480 C (118.40 F) before returning it directly into the vascular system of the patient. Other extracorporeal circuit perfusion devices need to achieve ex vivo temperatures of 490 C (120.20 F). Animal studies require temperatures of 540 C (129.10 F) during the induction phase to achieve adequate target tissue temperatures. Safety in such prior art is therefore limited by the incipient destruction of surrounding tissues at the sites of the high temperature phases of heating. When lesser temperatures are attempted, effectiveness is compromised by either inadequate temperatures or duration of heating or development of thermotolerance. As a result, only regional hyperthermia has been widely used clinically and only in combination with more traditional techniques such as radiation and chemotherapy. Presently, none of the known heating technologies provide clinically safe and effective hyperthermia to treat systemic or disseminated disease. In order for systemic hyperthermia to become more widely used clinically, current heating methods must also overcome the use of labor intensive, complex equipment, including invasive extracorporeal infusion and it's related toxicity problems to interposed tissues. Further, new hyperthermic technology must be compatible with noninvasive, real time thermometry.